

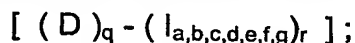
CLAIMS

1. Compounds of general formula (E) below :



5 in which :

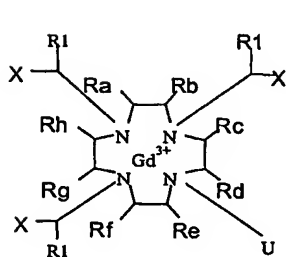
- B is a biovector
- L is a linker
- HR Ch represents a chelate of formula (I) :



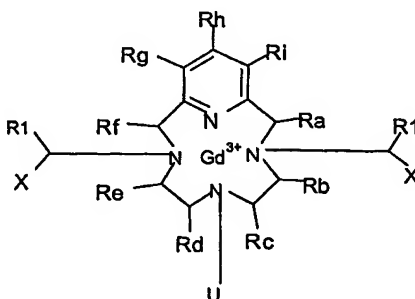
10 with :

a) $I_{a,b,c,d,e,f,g}$ chosen from $I_a, I_b, I_c, I_d, I_e, I_f, I_g,$

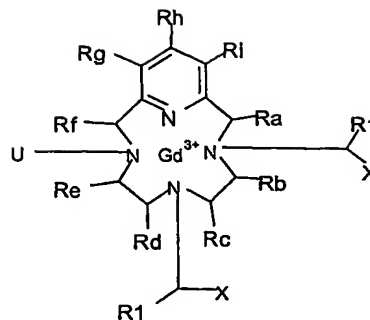
I_a, I_b, I_c having the meanings :



Ia



Ib



Ic

where :

- the X, which may be identical or different, are chosen from $CO_2R'_a$, $CONR'_bR'_c$ or $P(R'_d)O_2H$, with :

R'_a, R'_b and R'_c , which may be identical or different, representing H or (C_1-C_8) alkyl, which is optionally hydroxylated ;

P is the phosphorus atom, R'_d is chosen from OH, (C_1-C_8) alkyl or (C_1-C_8) alkoxy, (C_1-C_8) arylalkyl or (C_1-C_8) alkoxyalkyl ;

- R1 represents a hydrophilic group of molecular weight greater than 200, selected from groups :

- polyoxy(C₂-C₃)alkylene, in particular polyethylene glycol and its C₁-C₃ monoethers and monoesters, preferably of molecular mass from 1000 to 2000

- polyhydroxyalkyl

- polyol

- (R₂g)_e [(R₂g)_iR₃]_h where:

- h = 1 or 2 ; i = 0, 1 or 2 ; e = 1 to 5

- R₂ represents (the R₂ being identical or different) :

- nothing, an alkylene, an alkoxyalkylene, a polyalkoxyalkylene;

- a phenylene, or a heterocyclic residue which may be saturated or unsaturated, optionally substituted with OH, Cl, Br, I, (C₁-C₈)alkyl, (C₁-C₈)alkyloxy, NO₂, NR_xR_y, NR_xCOR_y, CONR_xR_y or COOR_x, R_x and R_y being H or (C₁-C₈)alkyl, and the linear, branched or cyclic C₁-C₁₄ alkyl, alkylene and alkoxy groups possibly being hydroxylated ;

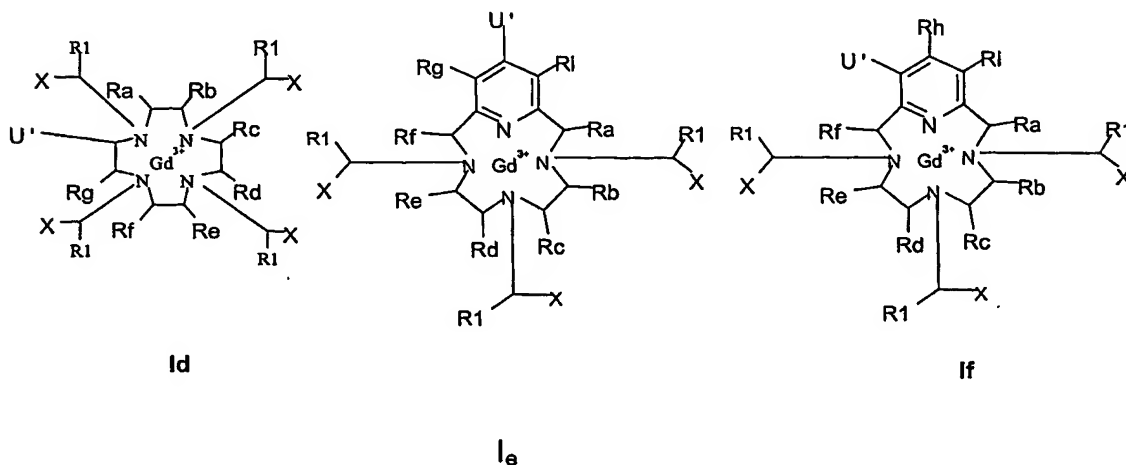
- g represents (the g being identical or different): nothing or a function O, CO, OCO, COO, SO₃, OSO₂, CONR', NR'CO, NR'COO, OCONR', NR', NR'CS, CSNR', SO₂NR', NR'SO₂, NR'CSO, OCSNR', NR'CSNR', P(O)(OH)NR', NR'P(O)-(OH), in which R' is H, (C₁-C₈)alkyl or R₃;

- R₃ represents alkyl, phenyl, alkyl substituted or interrupted with one or more phenyl groups, alkyleneoxy groups; amino or amido unsubstituted or substituted with alkyl optionally substituted or interrupted with one of the above groups; phenyl, phenylene and heterocyclic groups which may be substituted with OH, Cl, Br, I,

(C₁-C₈)alkyl, (C₁-C₈)alkyloxy, NO₂, NR_XR_Y, NR_XCOR_Y,
CONR_XR_Y or COOR_X, R_X and R_Y being H or (C₁-C₈)alkyl,
and linear, branched or cyclic C₁-C₁₄ alkyl, alkylene and
alkoxy groups which may be hydroxylated;

- R_a to R_i independently represent H, alkyl, hydroxyalkyl, alkylphenyl
or cycloalkyl.
- U is a group -CXR₄-linker 1, CHR₄CON-linker 1, CHR₄-CHR₅OH-
linker 1
- R₄ and R₅ independently representing H, alkyl or hydroxyalkyl,
- X having the meaning above,
- linker 1 being the linker providing the link between a chelate I_a, b,
c, and the linker L when q=0 and between I_a, b, c, and D when
q=1

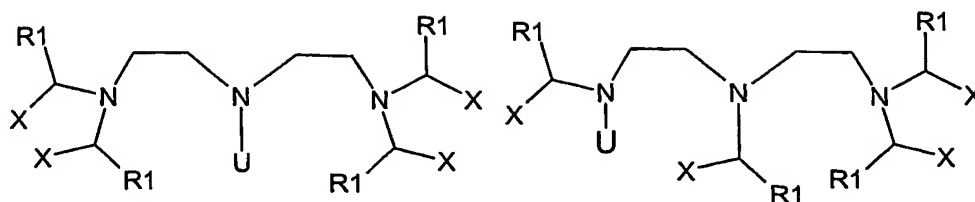
I_d, I_e, I_f having the meanings :



- X, R₁, R_a to R_i having the same meaning as above,
- U' is linker 1, providing the link between a chelate I_{d,e,f} and a linker
L when q=0 and between I_{d,e,f} and D when q=1,

- I_g representing

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U, X, R1 having the same meaning as above, linker 1 providing the link between a chelate I_g and a linker L when $q=0$ and between I_g and D when $q=1$.

5

b)

- $q = 0$ or $q=1$ - $r=1$ when $q=0$, or r is between 2 and 5 when $q=1$

10

c) D is a polyfunctional molecule capable of linking a linker L to at least two chelates $I_{a,b,c,d,e,f,g}$

d) x , y and z are between 1 and 8, preferably $x=1$ to 3, $y=1$ to 6, $z=1$ to 3, given that $y=z$;

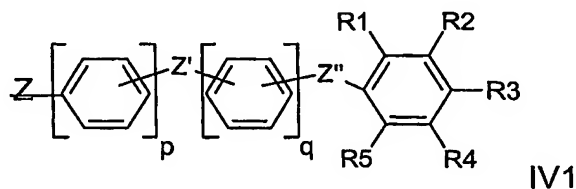
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and also the salts of the compounds of formula (E) with pharmaceutically acceptable inorganic or organic acids or bases.

2. Compound according to Claim 1, characterized in that R1 is $(CH_2)_xCONHR$ with $x=1, 2$ or 3 and R is a hydrophilic group of molecular weight greater than 200, chosen from :

20

1) a group:



25

and Z is a bond, CH_2 , CH_2CONH or $(CH_2)_2NHCO$

Z' is a bond, O, S, NQ, CH₂, CO, CONQ, NQCO, NQ-CONQ or CONQCH₂CONQ,

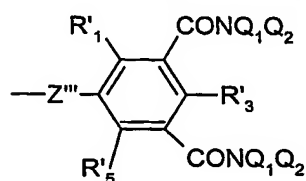
Z'' is a bond, CONQ, NQCO or CONQCH₂CONQ

p and q are integers, the sum of which is 0 to 3 ;

5 R₁, R₂, R₃, R₄ or R₅ represent:

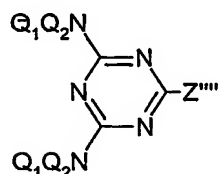
- either, independently of one another, H, Br, Cl, I, CONQ₁Q₂ or NQ₁COQ₂ with Q₁ and Q₂, which may be identical or different, being H or a (C₁-C₈)alkyl group which is mono- or polyhydroxylated or optionally interrupted with one or more oxygen atoms, and at least one and no more than two of R₁ to R₅ are CONQ₁Q₂ or NQ₁COQ₂ ;

- or R₂ and R₄ represent



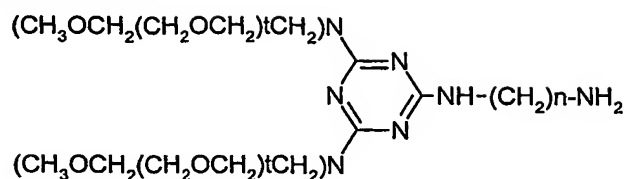
and R₁, R'₁, R₃, R'₃, R₅ and R'₅, which may be identical or different, represent H, Br, Cl or I, Q₁ and Q₂ have the same meaning as above and Z''' is a group chosen from CONQ, CONQCH₂CONQ, CONQCH₂, NQCONQ and CONQ(CH₂)₂NQCO and Q is H or (C₁-C₄)alkyl, which is optionally hydroxylated, it being possible for the alkyl groups to be linear or branched ;

2) a "flash" branch

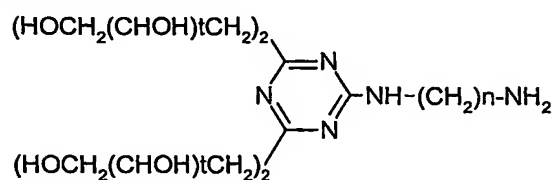


with Z''' being NQ(CH₂)_i(CH₂OCH₂)_j(CH₂)_jNH₂ with i = 2 to 6 and j = 1 to 6,

preferably



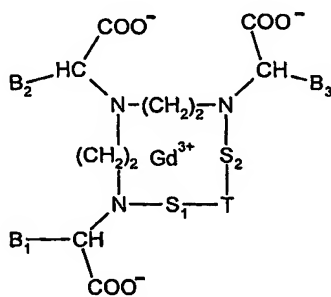
or



5 with $t = 1, 2, 3$ or 4 and $n = 2$ to 6 .

3. Compound according to Claim 1 or 2, characterized in that $q = 1$.

4. Compound according to Claim 1 or 2, characterized in that HR-CH
10 represents the group :

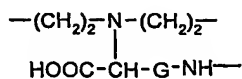


II 1.

in which :

$-\text{S}_1-\text{T}-\text{S}_2-$ is

1) either



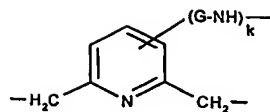
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where $\text{S}_1 = \text{S}_2 = (\text{CH}_2)_2$

with all three of B_1 , B_2 and B_3 representing $(\text{CH}_2)_x\text{CONHR}$ with

$x = 1, 2$ or 3

2) or

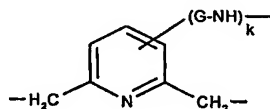


III₁

with $k = 0$ and $S_1 = S_2 = \text{CH}_2$

5 one of B₁, B₂, B₃ representing G-NH, and the others representing $(\text{CH}_2)_x\text{CONHR}$

3) or



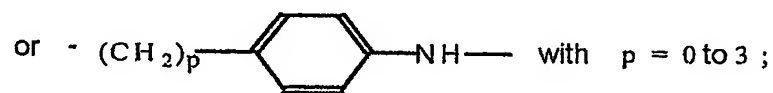
III₁

with $k=1$

all three of B₁, B₂, B₃ representing $(\text{CH}_2)_x\text{CONHR}$ with $x = 1, 2$ or 3

15 and GNH chosen from :

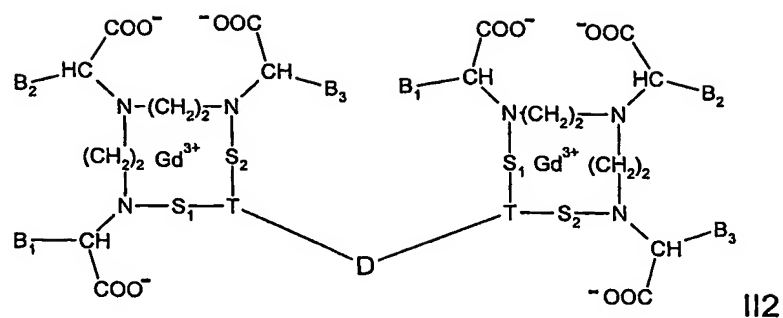
the groups $-(\text{CH}_2)_n\text{-NH-}$ with $n = 1$ to 4 ,



5. Compound according to Claim 3, characterized in that HR Ch
20 represents a group chosen from :

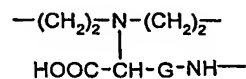
1) the group

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In which

$-S_1-T-S_2-$ is

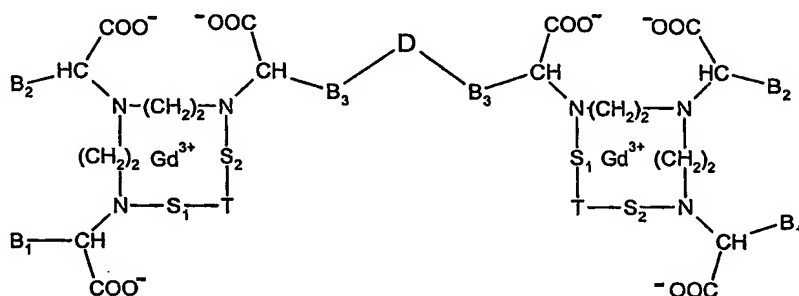


5

where $S_1 = S_2 = (\text{CH}_2)_2$

all three of B_1, B_2, B_3 representing $(\text{CH}_2)_x\text{CONHR}$ with $x = 1, 2$ or 3

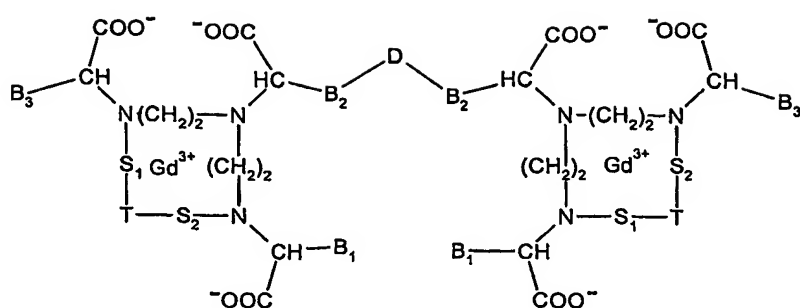
2) the group



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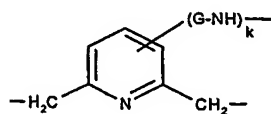
IIa2 (compound referred to as N-functionalized PCTA)

or IIb2 (compound referred to as N-functionalized PCTA and positional isomer of IIb2)



IIb2

5 in which S_1-T-S_2 is :



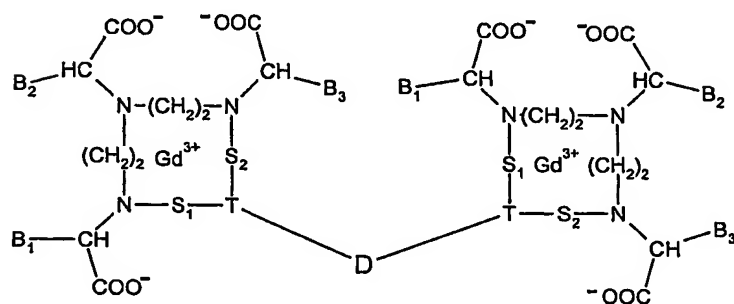
III2

with $k = 0$ and $S_1 = S_2 = CH_2$;

10 B_3 representing G-NH, and B_1 and B_2 representing $(CH_2)_xCONHR$ for IIa2

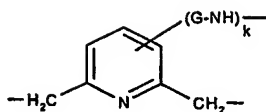
B_2 representing G-NH, and B_1 and B_3 representing $(CH_2)_xCONHR$ for IIb2

15 3) the group



IIc2 (compound referred to as C-functionalized PCTA)

when S_1 -T- S_2 - is :



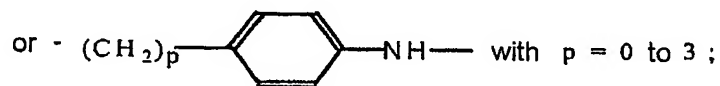
III₂

5 with $k = 1$ and $S_1 = S_2 = CH_2$;

all three of B_1 , B_2 , B_3 representing $(CH_2)_xCONHR$ with $x = 1, 2$ or 3
for IIc₂

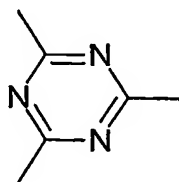
10 given that, for II₂, IIa₂, IIb₂ and IIc₂,

GNH is chosen from the groups $-(CH_2)_n-NH-$ with $n = 1$ to 4 ,



6. Compound according to any one of Claims 1 to 5, characterized in that
15 D is an aromatic backbone polyfunctionalized with carboxylate and/or
amino groups, D preferably being of 1,3,5-triazine type, of formula :

linker 2



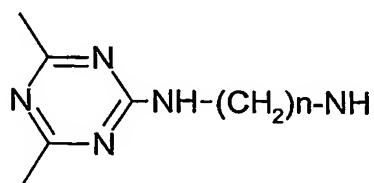
with linker 2 chosen from a) and b) and preferably a) :

20 **a)** $(CH_2)_2 - \phi - NH_2$, $(CH_2)_3 - NH_2$, $NH-(CH_2)_2-NH$, $NH-(CH_2)_3-NH$,

b) P1-I-P2, which may be identical or different, P1 and P2 being
chosen from OH, SH, NH_2 , nothing, CO_2H , NCS, NCO, SO_3H ,

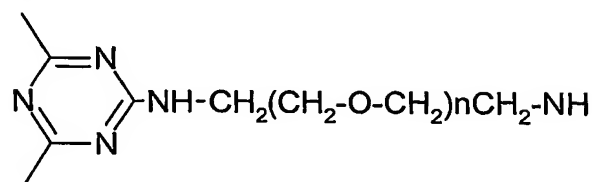
with I = alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene,

and D being more preferably :



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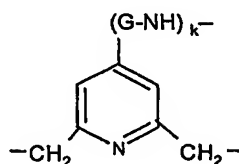
or



7. Compound according to any one of Claims 1 to 6, characterized in that
10 L is a linker chosen from polyoxyalkylenes, squaric acid, a squarate-PEG radical, an alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene.

8. Compound according to any one of Claims 3 to 7, in which x of
15 $(\text{CH}_2)_x\text{CONHR}$ is 2.

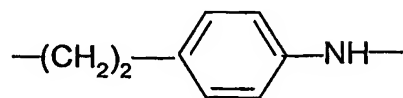
9. Compound according to any one of Claims 4 to 8, in which $-\text{S}_1 - \text{T} - \text{S}_2-$ represents:



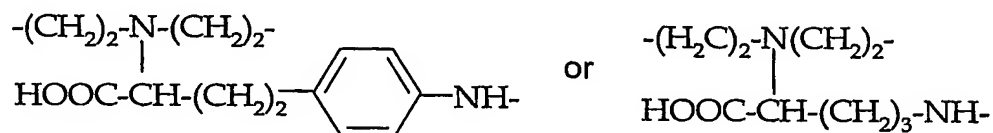
20 with $\text{S}_1 = \text{S}_2 = \text{CH}_2$.

10. Compounds according to Claim 9 of formula II1 in which k is 1 and G is $-(\text{CH}_2)_3-$.

11. Compounds according to Claim 9 of formula II1 in which k is 0 and B₂ or B₃ represents $-(\text{CH}_2)_3\text{NH}-$ or



12. Compound according to any one of Claims 4 to 9, in which $-\text{S}_1 - \text{T}$
5 $-\text{S}_2-$ represents:

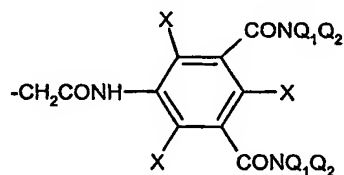


with $\text{S}_1 = \text{S}_2 = (\text{CH}_2)_2$.

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13. Compounds according to any one of the preceding claims, for which B₁, B₂ and B₃, when they do not represent $-\text{G}-\text{NH}$, represent $-(\text{CH}_2)_2\text{CONHR}$, with, in R, $p = q = 0$ and Z being $-\text{CH}_2\text{CONH}$.

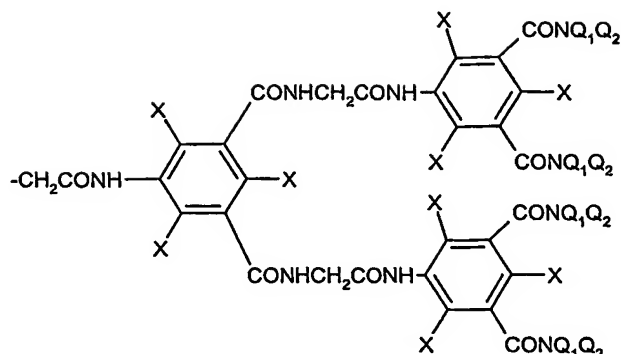
- 15 14. Compounds according to Claim 13, for which R represents:



and the X are identical and represent Br or I, while Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ contains from 4 to 10 hydroxyls in total.

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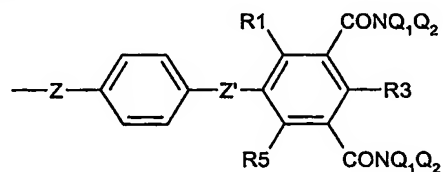
15. Compounds according to Claim 13, for which R represents:



and the X, which are identical, are Br or I, and Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ group contains from 4 to 10 hydroxyls in total.

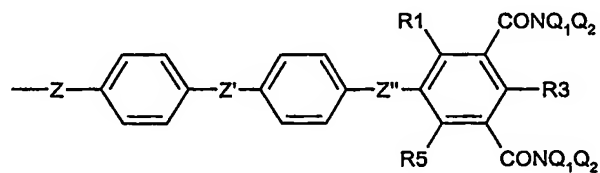
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16. Compounds according to any one of Claims 1 to 12, for which R represents:



10 Z is CH₂ or CH₂CONH, Z' is CONH or CONHCH₂CONH, R₁, R₃ and R₅, which are identical, are Br or I, and Q₁ and Q₂, which may be identical or different, are mono- or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ group contains from 4 to 10 hydroxyls in total.

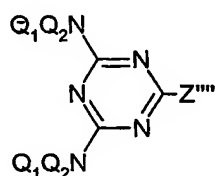
15 17. Compounds according to any one of Claims 1 to 12, for which R represents:



Z is CH₂CONH, Z' is CONH, Z'' is CONHCH₂CONH and R₁, R₃ and R₅, which are identical, are Br or I, and Q₁ and Q₂, which may be identical or different, are monohydroxylated or polyhydroxylated (C₁-C₈)alkyl groups such that each CONQ₁Q₂ group comprises from 4 to 10 hydroxyls in total.

5

18. Compounds according to any one of Claims 1 to 12, for which R represents

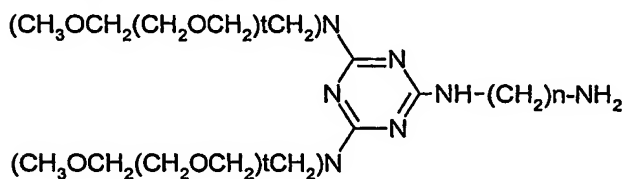


with Z''' being NQ(CH₂)_j(CH₂OCH₂)_i(CH₂)_jNH₂, with i = 2 to

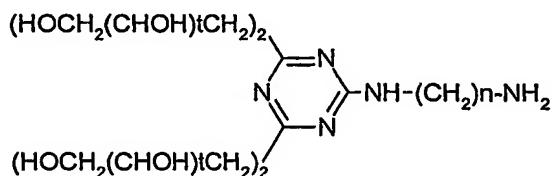
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6 and j = 1 to 6,

preferably R represents:



or



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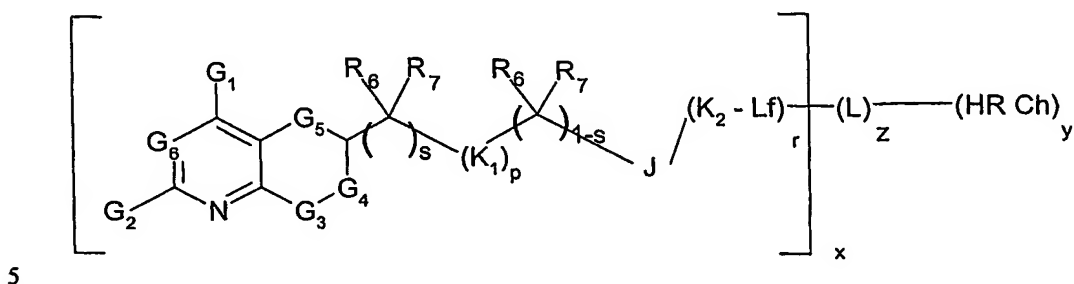
with t = 1, 2, 3 or 4 and n = 2 to 6.

19. Compound according to one of Claims 1 to 18, characterized in that the biovector is an agent capable of targeting cellular receptors or tissue components, in particular chosen from receptors of myocardial cells, of endothelial cells, of epithelial cells, of tumour cells or of immune system cells.

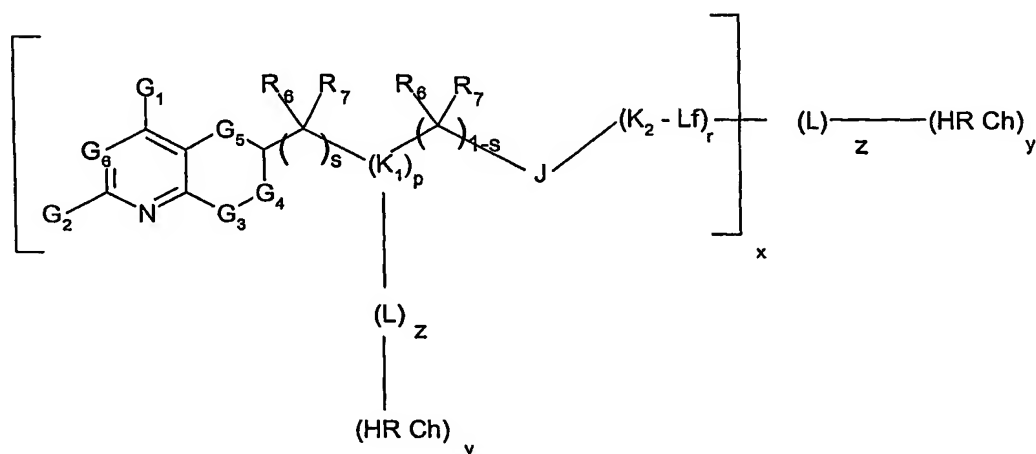
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20. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting a folate receptor, (E) being written :

(E1) :



or (E2) :



with :

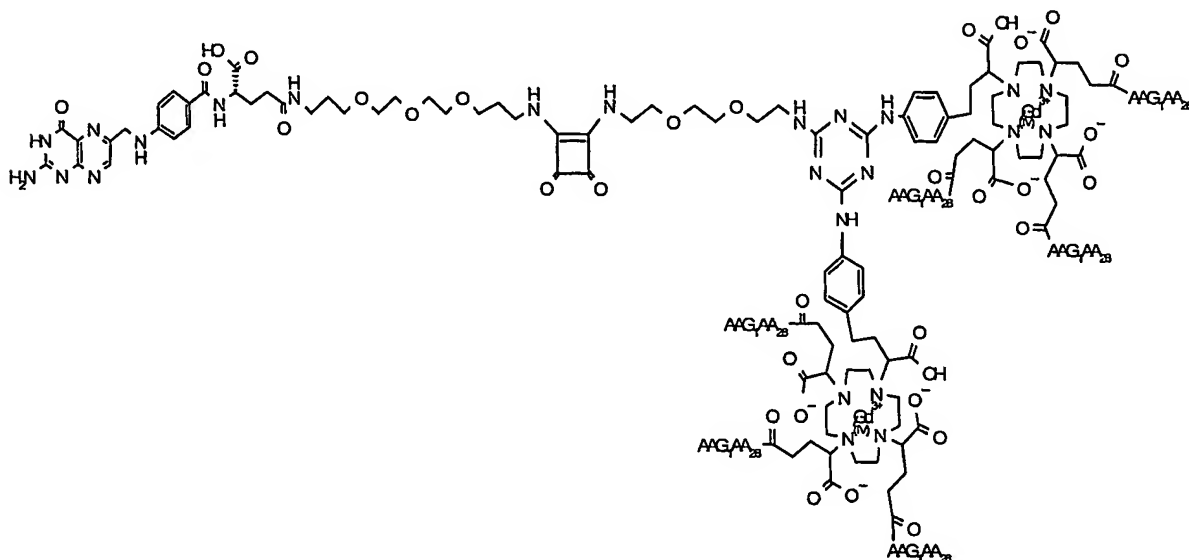
- a) G1 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, N R_f4 R_f5 ;
- b) G2 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, and N R_f4 R_f5 ;
- c) G3 and G4 represent divalent groups chosen independently from the group consisting of -(R_f6') C=, -N=, -(R_f6') C (R_f7')-, -N (R_f4')- ;
- d) G5 is absent or chosen from -(R_f6') C=, -N=, -(R_f6') C (R_f7')-, -N (R_f4')- ;
- e) the ring J is a possibly heterocyclic aromatic 5- or 6-membered ring, it being possible for the atoms of the ring to be C, N, O, S ;
- f) G6 is N or C ;

- g) K1 and K2 are chosen independently from the group consisting of - C (Z_f)-, -C (Z_f) O, -OC (Z_f)-, -N (R_{f4}'')-, -C (Z_f)-N (R_{f4}'')-, -N (R_{f4}'')-C (Z_f)-, -O-C(Z)-N(R_{f4}'')-, -N(R_{f4}'')-C(Z_f)-O-, N(R_{f4}'')-C(Z_f)-N(R_{f5}'')-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R_{f4}'')S(O)₂-, -C(R_{f6}'')(R_{f7}'')-,
 5 -N(C ≡ CH)-, -N(CH₂-C ≡ CH)-, C₁-C₁₂ alkyl and C₁-C₁₂ alkoxy; in which Z_f is O or S ; preferably K1 is -N(R_{f4}'')- or -C(R_{f6}'')(R_{f7}'')- with R_{f4}'', R_{f6}'', R_{f7}'' being H ; K2 possibly being covalently bonded to an amino acid ;
 h) R_{f1} is chosen from the group consisting of : H, halo, C₁-C₁₂ alkyl and C₁-C₁₂ alkoxy ; R_{f2}, R_{f3}, R_{f4}, R_{f4}', R_{f4}'', R_{f5}', R_{f5}'', R_{f6}' and R_{f7}' are chosen
 10 independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, C,-C, 2 alkanoyl, C,-C, 2 alkenyl, C₁-C₁₂ alkynyle, (C₁-C₁₂ alkoxy)carbonyl and (C,-C, 2 alkylamino)carbonyl;
 i) R_{f6} and R_{f7} are chosen independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy; or R_{f6} and R_{f7} together form O= ;
 15 j) R_{f6}' and R_{f7}' are chosen independently from the group consisting of : H, halo, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy ; or R_{f6}' and R_{f7}' together form O= ;
 k) L_f is a divalent linker which includes, where appropriate, a natural amino acid or a natural poly(amino acid), this acid or polyacid being bonded to K2 or to K1 via its alpha-amino group via an amide bond ;
 20 l) n, p, r and s are independently 0 or 1.

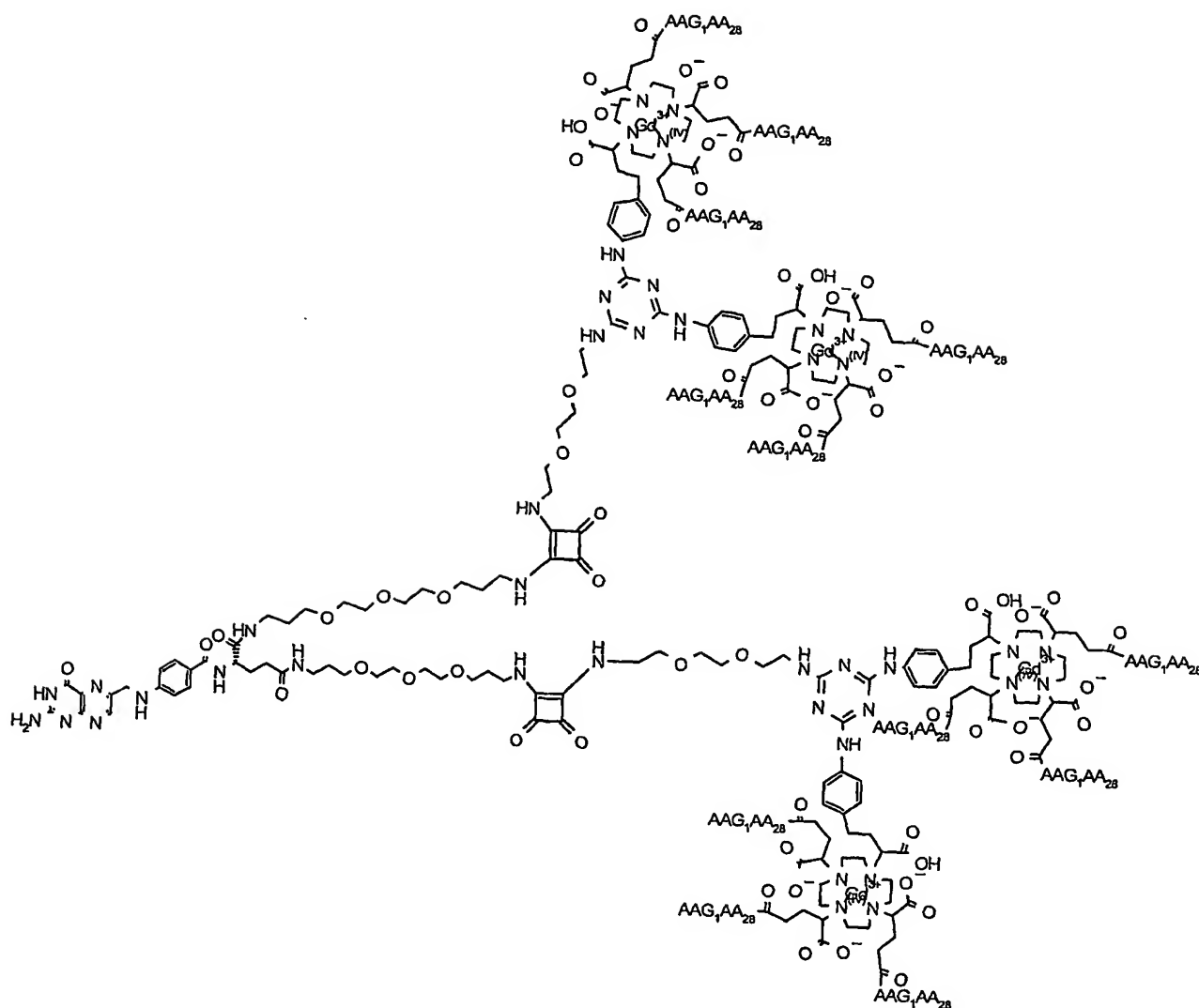
21. Compound according to Claim 20, characterized in that G1 is NH₂ or OH.

- 25 22. Compound according to Claim 20, characterized in that G3 is -N= or -CH- when the ring comprising G3 is aromatic, and G3 is -NH- or -CH₂- when the ring comprising G3 is non-aromatic ; with, preferably, G3 being -CH-, G1 being OH, G6 being NH and K1 being -N(R_{f4}'')-.

23. Compound according to Claim 20, characterized in that G4 is $-\text{CH}-$ or $-\text{C}(\text{CH}_3)-$ when the ring comprising G3 is aromatic, and $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$ when the ring comprising G3 is non-aromatic.
- 5 24. Compound according to Claim 20, characterized in that G5 is absent, with, preferably, G1 being OH, G2 being NH_2 , G6 being N.
25. Compound according to Claim 20, characterized in that G6 is N or C.
- 10 26. Compound according to Claim 20, characterized in that (E) is



or



27. Compound according to one of Claims 1 to 19, characterized in that the biovector is an angiogenesis inhibitor.

5

28. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of inhibiting the activity of an MMP.

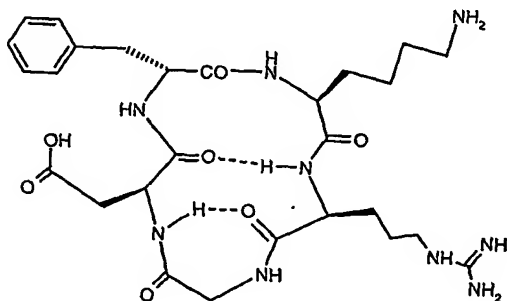
29. Compound according to Claim 28, characterized in that the biovector is an MMP inhibitor derived from ilomastat .

10

30. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting an integrin.

31. Compound according to Claim 30, characterized in that the biovector is
 5 an agent capable of targeting the integrin $\alpha v \beta 3$, in particular an RGD peptide, a peptidomimetic of the RGD peptide, or a non-peptide agent capable of mimicking the action of an RGD peptide.

32. Compound according to Claim 31, characterized in that the biovector is
 10 an RGDfV peptide having the structure :



33. Compound according to Claim 30, characterized in that the biovector is
 15 an agent capable of targeting the integrin GPIIb/IIIa.

34. Compound according to Claim 30, characterized in that the biovector is
 an agent capable of targeting a vitronectin.

35. Compound according to one of Claims 1 to 19, characterized in that
 20 the biovector is an agent capable of targeting an angiogenic receptor of endothelial cells, in particular a VEGFR receptor, preferably a peptide ATWLPPR or HTMYHHYQHHL.

36. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting receptors located on macrophages, in particular SRA receptors.

5 37. Compound according to Claim 36, characterized in that the biovector is a derivative of phosphatidylserine.

38. Compound according to one of Claims 1 to 19, characterized in that the biovector is a bisphosphonate derivative.

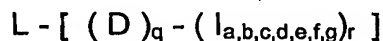
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39. Compound according to one of Claims 1 to 19, characterized in that the biovector is a peptide targeting tuftsin.

40. Compound according to one of Claims 1 to 19, characterized in that the biovector is Annexin 5.

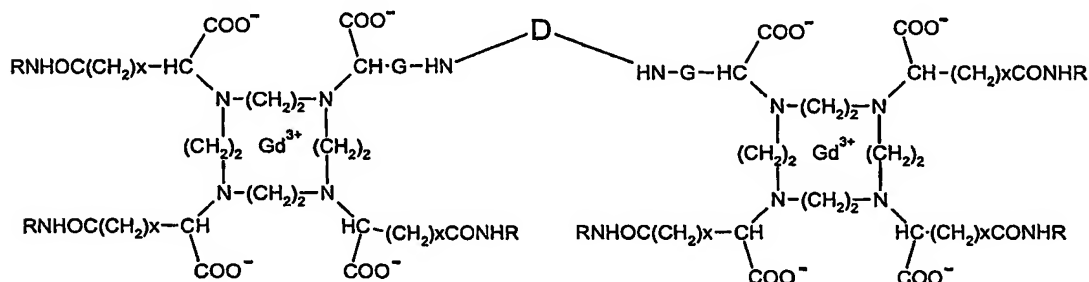
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41. Intermediate compound, used for preparing a compound according to Claim 1, of formula:



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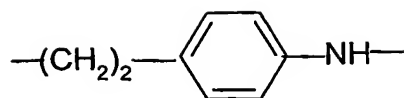
with L preferably of squarate type, $q=1$ and $[(D)_q - (I_{a,b,c,d,e,f,g})_r]$ preferably being chosen from :



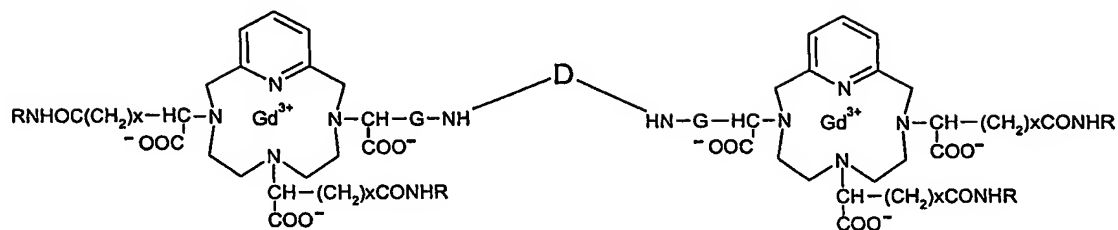
II' 2

25 with -G-NH being $-(CH_2)_3-NH-$ or

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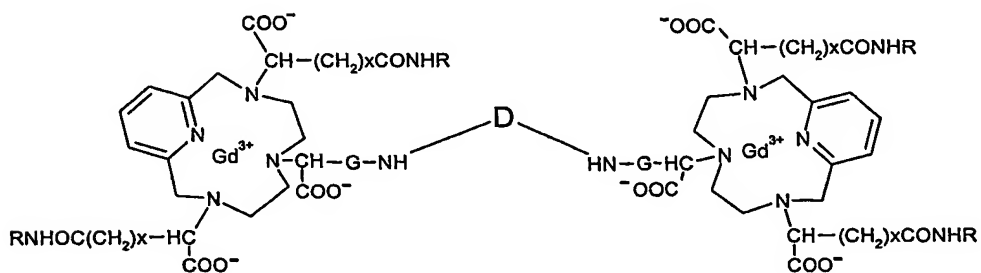
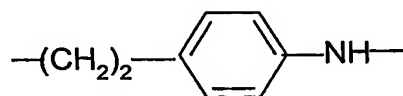
2)



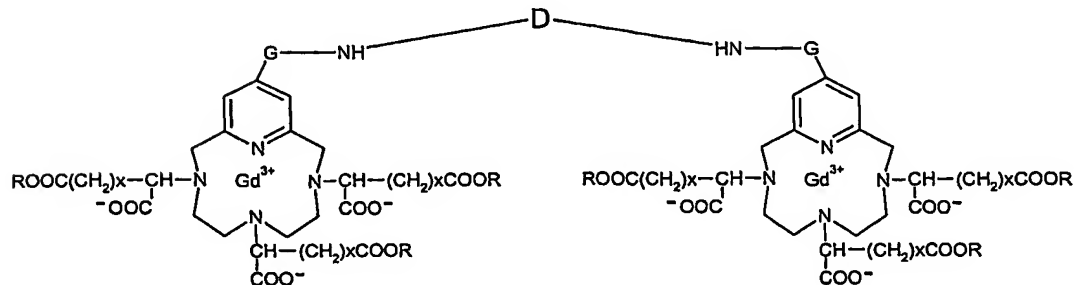
II" a2

5

3) II " b2

10 with -G-NH being $-(\text{CH}_2)_3-\text{NH}-$ or

4)



II "" 2

with G-NH being $-(\text{CH}_2)_3\text{-NH}$.

5 42. Compound according to any one of Claims 1 to 40, in its form bonded to an element M, (E) being written $\text{B}_x - \text{L} - (\text{HR Ch})_y - \text{M}$; given that M is either a paramagnetic metal ion having the atomic number 21-29, 42-44, or 58-70, or a radionuclide, typically chosen from ^{99}Tc , ^{117}Sn , ^{111}In , ^{97}Ru , ^{67}Ga , ^{68}Ga , ^{89}Zr , ^{177}Lu , ^{47}Sc , ^{105}Rh , ^{188}Re , ^{60}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{90}Y ,
10 ^{159}Gd , ^{149}Pr , and ^{166}Ho , or a heavy metal ion having the atomic number 21-31, 39-49, 50, 56-80, 82, 83 or 90.

43. Magnetic resonance imaging contrast product, characterized in that it comprises a compound according to one of Claims 1 to 40, optionally
15 combined with a pharmaceutically acceptable vehicle.

44. Contrast product according to Claim 43, provided in the form of an injectable sterile solution.

20 45. Compound according to either one of Claims 43 and 44, for its use in the diagnosis of a cardiovascular, cancer-related or inflammatory pathology.

25 46. Nuclear medicine product, characterized in that it comprises a compound according to one of Claims 1 to 38, optionally combined with a pharmaceutically acceptable vehicle.

47. Compound according to any one of Claims 1 to 22, having a relaxivity of between 25 and 200 $\text{mM}^{-1}\text{Gd}^{-1}$.

48. Method for preparing a compound according to any one of Claims 1 to 40 characterized in that it comprises the coupling of at least one biovector and at least one high-relaxivity chelate as defined in one of Claims 1 to 18.